

WHAT IS CLAIMED IS:

1. A method of treating rheumatoid arthritis which comprises delivery of a DNA sequence within a mammalian host, said DNA sequence expressing a biologically active gene product such that said biologically active gene product imparts systemic relief from

5 rheumatoid arthritis.

2. The method of claim 1 wherein said DNA sequence is delivered systemically within said mammalian host.

3. The method of claim 1 wherein said DNA sequence is delivered locally within mammalian host.

10 4. The method of claim 2 wherein said DNA sequence encodes an interleukin-1 receptor antagonist protein or a biologically active fragment thereof.

5. The method of claim 4 wherein said DNA sequence is transfected into a hematopoietic cell-containing population.

15 6. The method of claim 5 wherein said hematopoietic cell-containing population comprises bone marrow cells.

7. The method of claim 5 wherein said hematopoietic cell-containing population comprises CD34<sup>+</sup> blood leukocytes.

8. The method of claim 4 wherein the DNA sequence is transduced into peripheral blood cells.

20 9. The method of claim 8 wherein said peripheral blood cells are lymphocytes.

10. The method of claim 4 wherein said DNA sequence is subcloned into a viral vector selected from the group consisting of a retroviral vector, an adenovirus vector,

an adeno-associated vector, a herpes simplex virus vector, an SV40 vector, a polyoma virus vector, a papilloma virus vector, a picornavirus vector, and a vaccinia virus vector.

11. The method of claim 10 wherein said DNA sequence is transduced into a hematopoietic cell-containing population.

5 12. The method of claim 11 wherein said hematopoietic cell-containing population comprises bone marrow cells.

13. The method of claim 11 wherein said hematopoietic cell-containing population comprises CD34<sup>+</sup> blood leukocytes.

14. The method of claim 10 wherein the DNA sequence is transduced into peripheral blood cells.

10 15. The method of claim 14 wherein said peripheral blood cells are lymphocytes.

16. The method of claim 10 wherein said viral vector is a retroviral vector.

17. The method of claim 16 wherein said retroviral vector is transduced into a hematopoietic cell-containing population.

15 18. The method of claim 17 wherein said hematopoietic cell-containing population comprises bone marrow cells.

19. The method of claim 17 wherein the hematopoietic cell-containing population comprises CD34<sup>+</sup> blood leukocytes.

20 20. The method of claim 16 wherein the DNA sequence is transduced into peripheral blood cells.

21. The method of claim 20 wherein said peripheral blood cells are lymphocytes.

22. The method of claim 16 wherein said retroviral vector is MFG-IRAP.

23. The method of claim 22 wherein MFG-IRAP is used to transduce a hematopoietic cell-containing population.

24. The method of claim 23 wherein said hematopoietic cell-containing population comprises bone marrow cells.

5 25. The method of claim 23 wherein said hematopoietic cell-containing population comprises CD34<sup>+</sup> blood leukocytes.

26. The method of claim 22 wherein the DNA sequence is transduced into peripheral blood cells.

27. The method of claim 26 wherein said peripheral blood cells are lymphocytes.

10 28. The method of claim 3 wherein said DNA sequence encodes an interleukin-1 receptor antagonist protein or a biologically active fragment thereof.

29. The method of claim 28 wherein said DNA sequence is transfected into *in vitro* cultured myoblast cells and transplanted into said mammalian host.

15 30. The method of claim 29 wherein said DNA sequence is subcloned into a non-viral vector.

31. The method of claim 30 wherein said non-viral vector is a plasmid DNA vector.

32. The method of claim 29 wherein said DNA sequence is subcloned into a viral vector.

20 33. The method of claim 32 wherein said DNA sequence is subcloned into a retroviral vector.

34. The method of claim 33 wherein said retroviral vector is MFG-IRAP.

35. The method of claim 28 wherein said DNA sequence is injected directly into skeletal muscle of said mammalian host.

36. The method of claim 35 wherein said DNA sequence is subcloned into a non-viral vector.

5 37. The method of claim 36 wherein said non-viral vector is a plasmid DNA vector.

38. The method of claim 35 wherein said DNA sequence is subcloned into a viral vector.

39. The method of claim 38 wherein said DNA sequence is subcloned into a retroviral vector.

10 40. The method of claim 39 wherein said retroviral vector is MFG-IRAP.

41. The method of claim 2 wherein said DNA sequence encodes a cytokine or biologically active fragment thereof selected from the group consisting of interleukin-4 and interleukin-10.

15 42. The method of claim 2 wherein said DNA sequence encodes a soluble cytokine receptor or biologically active fragment thereof selected from the group consisting of a soluble interleukin-1 receptor and a tumor necrosis factor- $\alpha$  soluble receptor.

43. The method of claim 2 wherein said DNA sequence encodes TIMP or a biologically active fragment thereof.

20 44. The method of claim 2 wherein said DNA sequence encodes an anti-adhesion molecule or a biologically active fragment thereof selected from the group consisting of soluble ICAM-1, soluble CD44, and soluble CD18.

45. The method of claim 2 wherein said DNA sequence encodes superoxide dismutase or a biologically active fragment thereof.

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46. The method of claim 2 wherein said DNA sequence encodes a cartilage growth factor or a biologically active fragment thereof selected from the group consisting of IGF- $\alpha$  and TGF- $\beta$ .

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47. The method of claim 2 wherein said DNA sequence encodes collagen or a biologically active fragment thereof.

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48. The method of claim 3 wherein said DNA sequence encodes a cytokine or biologically active fragment thereof selected from the group consisting of interleukin-4 and interleukin-10.

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49. The method of claim 3 wherein said DNA sequence encodes a soluble cytokine receptor or biologically active fragment thereof selected from the group consisting of the soluble interleukin-1 receptor and the tumor necrosis factor- $\alpha$  soluble receptor.

50. The method of claim 3 wherein said DNA sequence encodes TIMP or a

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biologically active fragment thereof.

51. The method of claim 3 wherein said DNA sequence encodes an anti-adhesion molecule or a biologically active fragment thereof selected from the group consisting of soluble ICAM-1, soluble CD44, and soluble CD18.

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52. The method of claim 3 wherein said DNA sequence encodes superoxide

dismutase or a biologically active fragment thereof.

53. The method of claim 3 wherein said DNA sequence encodes a cartilage growth factor or a biologically active fragment thereof selected from the group consisting of IGF- $\alpha$  and TGF- $\beta$ .

5 54. The method of claim 3 wherein said DNA sequence encodes collagen or a biologically active fragment thereof.

10 55. A method of treating systemic lupus erythematosus which comprises delivery of a DNA sequence within a mammalian host, said DNA sequence expressing a biologically active gene product such that said biologically active gene product imparts systemic relief from systemic lupus erythematosus.

15 56. The method of claim 55 wherein said DNA sequence is delivered systemically within said mammalian host.

57. The method of claim 55 wherein said DNA sequence is delivered locally within said mammalian host.

15 58. The method of claim 56 wherein said DNA sequence encodes an interleukin-1 receptor antagonist protein or a biologically active fragment thereof.

59. The method of claim 58 wherein said DNA sequence is transduced into a hematopoietic cell-containing population.

60. The method of claim 59 wherein said hematopoietic cell-containing population are bone marrow cells.

20 61. The method of claim 59 wherein said hematopoietic cell-containing population comprise CD34 $^{+}$  blood leukocytes.

62. The method of claim 58 wherein the DNA sequence is transduced into peripheral blood cells.
63. The method of claim 62 wherein said peripheral blood cells are lymphocytes.
64. The method of claim 58 wherein said DNA sequence is subcloned into a viral vector selected from the group consisting of a retroviral vector, an adenovirus vector, an adeno-associated vector, a herpes simplex virus vector, an SV40 vector, a polyoma virus vector, a papilloma virus vector, a picornavirus vector, and a vaccinia virus vector.
- 5 65. The method of claim 64 wherein said DNA sequence is transduced into a hematopoietic cell-containing population.
- 10 66. The method of claim 65 wherein said hematopoietic cell-containing population comprises bone marrow cells.
67. The method of claim 65 wherein said hematopoietic cell-containing population comprises CD34<sup>+</sup> blood leukocytes.
- 15 68. The method of claim 64 wherein the DNA sequence is transduced into peripheral blood cells.
69. The method of claim 68 wherein said peripheral blood cells are lymphocytes.
70. The method of claim 64 wherein said viral vector is a retroviral vector.
- 20 71. The method of claim 70 wherein said retroviral vector is transfected into a hematopoietic cell-containing population.
72. The method of claim 71 wherein said hematopoietic cell-containing population comprises bone marrow cells.

73. The method of claim 71 wherein the hematopoietic cell-containing population comprises CD34<sup>+</sup> blood leukocytes.

74. The method of claim 70 wherein the DNA sequence is transduced into peripheral blood cells.

5 75. The method of claim 74 wherein said peripheral blood cells are lymphocytes.

76. The method of claim 70 wherein said retroviral vector is MFG-IRAP.

10 77. The method of claim 76 wherein MFG-IRAP is used to transduce a hematopoietic cell-containing population.

78. The method of claim 77 wherein said hematopoietic cell-containing population comprises bone marrow cells.

15 79. The method of claim 77 wherein said hematopoietic cell-containing population comprises CD34<sup>+</sup> blood leukocytes.

80. The method of claim 76 wherein the DNA sequence is transfected into peripheral blood cells.

15 81. The method of claim 80 wherein said peripheral blood cells are lymphocytes.

82. The method of claim 57 wherein said DNA sequence encodes an interleukin-1 receptor antagonist protein or a biologically active fragment thereof.

15 83. The method of claim 82 wherein said DNA sequence is transfected into *in vitro* cultured myoblast cells and transplanted into said mammalian host.

20 84. The method of claim 83 wherein said DNA sequence is subcloned into a non-viral vector.

85. The method of claim 84 wherein said non-viral vector is a plasmid DNA vector.

86. The method of claim 83 wherein said DNA sequence is subcloned into a viral vector selected from the group consisting of a retroviral vector, an adenovirus vector, an adeno-associated vector, a herpes simplex virus vector, an SV40 vector, a polyoma virus vector, a papilloma virus vector, a picornavirus vector, and a vaccinia virus vector.

5       87. The method of claim 86 wherein said DNA sequence is subcloned into a retroviral vector.

88. The method of claim 87 wherein said retroviral vector is MFG-IRAP.

89. The method of claim 82 wherein said DNA sequence is injected directly into skeletal muscle of said mammalian host.

10      90. The method of claim 89 wherein said DNA sequence is subcloned into a non-viral vector.

91. The method of claim 90 wherein said non-viral vector is a plasmid DNA vector.

15      92. The method of claim 89 wherein said DNA sequence is subcloned into a viral vector selected from the group consisting of a retroviral vector, an adenovirus vector, an adeno-associated vector, a herpes simplex virus vector, an SV40 vector, a polyoma virus vector, a papilloma virus vector, a picornavirus vector, and a vaccinia virus vector.

93. The method of claim 92 wherein said DNA sequence is subcloned into a retroviral vector.

94. The method of claim 93 wherein said retroviral vector is MFG-IRAP.

20      95. The method of claim 56 wherein said DNA sequence encodes a cytokine or biologically active fragment thereof selected from the group consisting of interleukin-4 and interleukin-10.

96. The method of claim 56 wherein said DNA sequence encodes a soluble cytokine receptor or biologically active fragment thereof selected from the group consisting of the soluble interleukin-1 receptor and the tumor necrosis factor- $\alpha$  soluble receptor.

5       97. The method of claim 56 wherein said DNA sequence encodes TIMP or a biologically active fragment thereof.

98. The method of claim 56 wherein said DNA sequence encodes an anti-adhesion molecule or a biologically active fragment thereof selected from the group consisting of soluble ICAM-1, soluble CD44, and soluble CD18.

10      99. The method of claim 56 wherein said DNA sequence encodes superoxide dismutase or a biologically active fragment thereof.

100. The method of claim 56 wherein said DNA sequence encodes a cartilage growth factor or a biologically active fragment thereof selected from the group consisting of IGF- $\alpha$  and TGF- $\beta$ .

101. The method of claim 56 wherein said DNA sequence encodes collagen or a 15     biologically active fragment thereof.

102. The method of claim 57 wherein said DNA sequence encodes a cytokine or biologically active fragment thereof selected from the group consisting of interleukin-4 and interleukin-10.

20      103. The method of claim 57 wherein said DNA sequence encodes a soluble cytokine receptor or biologically active fragment thereof selected from the group consisting of a soluble interleukin-1 receptor and a tumor necrosis factor- $\alpha$  soluble receptor.

104. The method of claim 57 wherein said DNA sequence encodes TIMP or a biologically active fragment thereof.

105. The method of claim 57 wherein said DNA sequence encodes an anti-adhesion molecule or a biologically active fragment thereof selected from the group consisting of  
5 soluble ICAM-1, soluble CD44, and soluble CD18.

106. The method of claim 57 wherein said DNA sequence encodes superoxide dismutase or a biologically active fragment thereof.

107. The method of claim 57 wherein said DNA sequence encodes a cartilage growth factor or a biologically active fragment thereof selected from the group consisting of  
10 IGF- $\alpha$  and TGF- $\beta$ .

108. The method of claim 57 wherein said DNA sequence encodes collagen or a biologically active fragment thereof.

109. A method of treating osteogenesis imperfecta which comprises delivery of a DNA sequence encoding collagen or a biologically active fragment thereof within a  
15 mammalian host so as to promote therapeutic relief from osteogenesis imperfecta.

110. The method of claim 109 wherein said DNA sequence is delivered systemically within said mammalian host.

111. The method of claim 110 wherein said DNA sequence is subcloned into a viral vector selected from the group consisting of a retroviral vector, an adenovirus vector,  
20 an adeno-associated vector, a herpes simplex virus vector, an SV40 vector, a polyoma virus vector, a papilloma virus vector, a picornavirus vector, and a vaccinia virus vector.

112. The method of claim 111 wherein said viral vector is a retroviral vector.

113. A method of treating osteoporosis which comprises delivery of a DNA sequence within a mammalian host, said DNA sequence expressing a biologically active gene product such that said biologically active gene product imparts systemic relief from osteoporosis.

5 114. The method of claim 113 wherein said DNA sequence is delivered systemically within said mammalian host.

10 115. The method of claim 114 wherein said DNA sequence is subcloned into a viral vector selected from the group consisting of a retroviral vector, an adenovirus vector, an adeno-associated vector, a herpes simplex virus vector, an SV40 vector, a polyoma virus vector, a papilloma virus vector, a picornavirus vector, and a vaccinia virus vector.

116. The method of claim 115 wherein said viral vector is a retroviral vector.

117. The method of claim 116 wherein said DNA sequence encodes a cytokine or biologically active fragment thereof selected from the group consisting of interleukin-1 receptor antagonist, interleukin-4 and interleukin-10.

15 118. The method of claim 116 wherein said DNA sequence encodes a soluble cytokine receptor or biologically active fragment thereof selected from the group consisting of a soluble interleukin-1 receptor, a tumor necrosis factor- $\alpha$  soluble receptor and a soluble interleukin-6 receptor.

20 119. The method of claim 116 wherein said DNA sequence encodes TIMP or a biologically active fragment thereof.

120. The method of claim 116 wherein said DNA sequence encodes an anti-adhesion molecule or a biologically active fragment thereof selected from the group consisting of soluble ICAM-1, soluble CD44, and soluble CD18.

5       121. The method of claim 116 wherein said DNA sequence encodes superoxide dismutase or a biologically active fragment thereof.

10      122. A method of treating a connective tissue disease or disorder selected from the group consisting of Sjögren's syndrome, polymyositis-dermatomyositis, systemic sclerosis, vasculitis syndromes, juvenile rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, osteoporosis, osteogenesis imperfecta, Paget's disease and inflammatory bowel disease which comprises delivery of a DNA sequence within a mammalian host, said DNA sequence expressing a biologically active gene product such that said biologically active gene product imparts systemic relief from said connective tissue disease or disorder.

15      123. The method of claim 122 wherein said viral vector is a retroviral vector.

20      124. The method of claim 123 wherein said DNA sequence encodes a cytokine or biologically active fragment thereof selected from the group consisting of interleukin-1 receptor antagonist, interleukin-4 and interleukin-10.

25      125. The method of claim 123 wherein said DNA sequence encodes a soluble cytokine receptor or biologically active fragment thereof selected from the group consisting of a soluble interleukin-1 receptor, a tumor necrosis factor- $\alpha$  soluble receptor and a soluble interleukin-6 receptor.

30      126. The method of claim 123 wherein said DNA sequence encodes TIMP or a biologically active fragment thereof.

127. The method of claim 123 wherein said DNA sequence encodes an anti-adhesion molecule or a biologically active fragment thereof selected from the group consisting of soluble ICAM-1, soluble CD44, and soluble CD18.

5 128. The method of claim 123 wherein said DNA sequence encodes superoxide dismutase or a biologically active fragment thereof.

129. The method of claim 123 wherein said DNA sequence encodes a cartilage growth factor or a biologically active fragment thereof selected from the group consisting of IGF- $\alpha$  and TGF- $\beta$ .

10 130. The method of claim 123 wherein said DNA sequence encodes collagen or a biologically active fragment thereof.

131. A mammalian cell comprising a recombinant retroviral vector wherein said recombinant retroviral vector comprises a DNA sequence encoding IRAP or a biologically active fragment thereof.

15 132. A mammalian cell of claim 131 wherein said recombinant retroviral vector is derived from a Moloney murine leukemia virus.

133. A mammalian cell of claim 132 where said DNA sequence encoding IRAP or a biologicall active fragment thereof consists essentially of SEQ ID NO:2.

134. A mammalian cell of claim 133 wherein said recombinant retroviral vector is MFG-IRAP.

20 135. The mammalian cell of claim 131 which is a hematopoietic cell.

136. The mammalian cell of claim 132 which is a hematopoietic cell.

137. The mammalian cell of claim 133 which is a hematopoietic cell.

138. The mammalian cell of claim 134 which is a hematopoietic cell.
139. The hematopoietic cell of claim 135 which is a bone marrow cell.
140. The hematopoietic cell of claim 136 which is a bone marrow cell.
141. The hematopoietic cell of claim 137 which is a bone marrow cell.
- 5 142. The hematopoietic cell of claim 138 which is a bone marrow cell.

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